Cardiometabolic Changes and Disparities Among Persons With Spinal Cord Injury: A 17-Year Cohort Study

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Background: Cardiometabolic syndrome in individuals who are aging with spinal cord injury (SCI) increases the risk of cardiovascular disease and diabetes. Longitudinal research is needed on the natural progression of cardiometabolic syndrome in SCI. **Objective:** To identify the magnitude of changes in biomarkers of cardiometabolic syndrome and diabetes over time in people aging with SCI, and to discern how these biomarkers relate to demographics of race/ethnicity and sex. **Methods:** This cohort study was a follow-up of a convenience sample of 150 participants (mean age, 51.3; duration of SCI, 27.3 years) from a full cohort of 845 who participated in research in which physiologic and serologic data on cardiovascular disease had been prospectively collected (1993-1997). Inclusion criteria were adults with traumatic-onset SCI. Average years to follow-up were 15.7 ± 0.9. Assessments were age, race, level and completeness of injury, duration of injury, blood pressure, body mass index, waist circumference, serum lipids, fasting glucose, hemoglobin A1c, and medications used. Primary outcome was meeting at least 3 of the criteria for cardiometabolic syndrome. **Results:** The frequency of cardiometabolic syndrome increased significantly from 6.7% to 20.8% or 38.2% according to 2 definitions. It was significantly higher in Hispanics and apparently higher in women. Diabetes increased significantly by a factor of 6.7. **Conclusion:** Our data indicate clinically important increases in the frequency of cardiometabolic syndrome, especially among Hispanic and female participants, and a similar increase in diabetes among individuals aging with SCI. Clinical practice guidelines need to be customized for women and Hispanics with SCI. **Key words:** *aging, cardiovascular disease, diabetes, dyslipidemia, metabolic syndrome, risk factors*

Cardiometabolic syndrome comprises a set of interrelated risk factors for cardiovascular disease and diabetes.[1,2] These risks are an escalating problem for people with spinal cord injury (SCI).[3-10] The main causes of cardiometabolic syndrome in persons with SCI are diet and fitness level.[9] Overfeeding during initial rehabilitation can become habitual, and the effect is amplified by a lowered metabolic rate and muscle atrophy.[9] The resulting weight gain and metabolic changes are difficult to reverse by exercise alone.[11] The SCI population is aging. Consequently, cardiometabolic syndrome in people who are aging with SCI presents substantial challenges.

The risk of cardiometabolic syndrome in SCI in the United States is as high as 58% for those who are relatively young, predominantly nonsmoking, and with intact adrenergic systems.[12] The prevalence of cardiometabolic syndrome is 34% in individuals with SCI in the United States,[12] with low high-density lipoprotein (HDL) cholesterol in 76%, high triglycerides in 68%, and hypertension in 29% of patients studied.[12] The National Cholesterol Education Project's Adult Treatment Panel III Guidelines provide a 4-step sequential algorithm for customized management of dyslipidemia and cardiovascular disease.[13] Lipid-lowering interventions were indicated in 63% of SCI patients studied, yet at the time of the study none of the patients had received such intervention.[12] Consequently, new evidence-based clinical practice guidelines are in development.[14] Guidelines for the prevention and

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treatment of cardiometabolic syndrome must take into account both the natural progression of the syndrome and disparities in underserved and disadvantaged populations. Gaps in existing research suggest a need for longitudinal studies that characterize the natural progression of cardiometabolic syndrome in the SCI population and that assess the risk factors associated with its progression in disparate demographic groups. In the able-bodied, disparities associated with race/ethnicity include higher rates of coronary artery disease and/or diabetes among Blacks, Hispanics, and Asians/Pacific Islanders.[15-17] Cardiometabolic disparities associated with race/ethnicity are probably related to nutrition that is linked to culture, which may be influenced by socioeconomic status, and to genetic adaptations coupled with cultural nutritional history. Racial/ethnic cardiometabolic disparities may also be influenced by restricted access to health care associated with poverty. Cardiometabolic disparities related to sex are primarily influenced by ignorance in medical practice,[18-21] because screening, diagnostics, treatment, and research have been primarily focused on men.

Our purpose was to characterize the natural progression of cardiometabolic disease in persons aging with SCI. The 2 objectives were to identify the magnitude of changes in cardiometabolic syndrome and overt diabetes status over 17 years in a cohort of 150 outpatients with chronic SCI, and to identify how these changes relate to demographics of race/ethnicity and sex.

Methods

Participants

This is a 17-year follow-up of a full cohort of 845 individuals with SCI who first participated between 1993 and 1997 (the methods have been previously published).[22] The full cohort comprised serial cases completing annual physical examinations in an outpatient clinic across approximately 3 years. All participants were adults with traumatic onset SCI.

Data collection procedures

We performed extensive procedures to identify all potential participants. We also searched the patient appointment-scheduling database for the last clinical appointments, hospitalizations, known addresses, and telephone numbers to obtain updated information on all potential participants.

Recruitment for the follow-up study began on March 11, 2011. After obtaining institutional review board approval, we sent a general letter announcing the follow-up study to all former participants believed to be alive, reminding them of their previous participation and describing the follow-up assessment. Those agreeing to participate were scheduled for clinical assessment. Participants received $150 as compensation for completing the assessment and to cover expenses to get to the clinic.

Follow-up data were collected from August 18, 2011 to February 6, 2013. We evaluated participants in the approximate order in which they were first enrolled. However, some priority was given to older participants and those with the most severe neurologic deficits (C4 and higher). Data were collected primarily in a clinical research space that is fully assessable to individuals with disabilities. After informed consent was obtained, fasting participants were asked to fill out a questionnaire, after which they underwent a physical examination and had a blood sample taken from a superficial arm vein.

Follow-up measures

Participants were asked to bring in all prescription medication containers to document current medications. Cardiometabolic syndrome was defined as meeting at least 3 of the criteria defined in **Table 1**. Participants were assisted (as necessary) to get on the exam table and were allowed to rest for 15 minutes before vital signs were measured. Systolic and diastolic blood pressure measurements were made using a standard protocol (Hypertension Detection and Follow-up Program Cooperative Group, 1978). Three supine blood pressure readings were completed, and average systolic and diastolic blood pressures were computed from the second and third readings. Waist circumference, a surrogate measure of visceral adipose tissue and cardiovascular disease risk in men and women with SCI,[23] was measured at the narrowest point between the ribs and

Table 1. Criteria for definition of cardiometabolic syndrome with at least 3 risk factors present

Measure	Risk factor cutoff
Central obesity	
Body mass index	≥30 kg/m^2
Or	
Waist circumference[a]	
Men	>40 in.
Women	>35 in.
Fasting serum triglycerides	>150 mg/dL
Fasting serum HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure[b]	>130/85 mm Hg
Fasting plasma glucose	>100 mg/dL

Note: Criteria adapted from the American Heart Association/National Heart Lung and Blood Institute/National Cholesterol Education Project's Adult Treatment Panel (2004) definition. HDL = high-density lipoprotein.

[a]Alternative measure of the central obesity risk factor added for the follow-up assessment but not measured in the baseline assessment of the same sample.

[b]Additional risk factor measured for the follow-up assessment but not measured in the baseline assessment of the same sample.

the iliac crest. Blood specimen collection and processing for total serum cholesterol, HDL, low-density lipoprotein (LDL), triglycerides, fasting glucose, and hemoglobin A1c was drawn using standard phlebotomy techniques in the morning. Venous access was attempted a maximum of 3 times. If the phlebotomist was unable to gain peripheral intravenous access, serum biomarkers were not collected. If inadequate blood volume was obtained, the specimen was used to maximize the potential number of biomarkers that could be measured from the volume collected. All specimens were analyzed in the same laboratory as the baseline data.

Diabetes can be defined by 4 alternative measures: fasting glucose values of >126 mg/dL, hemoglobin A1c > 6.5%, oral glucose tolerance test, or medications. For the full cohort baseline sample (N = 845), only fasting glucose was recorded. For follow-up (N = 150), hemoglobin A1c and medications were recorded and used for a second diagnosis.

Statistical analysis

Selective attrition

Participants were classified in 1 of 3 groups: participants, known deceased, and nonrespondents (did not respond or could not be found). One-way analysis of variance was used to compare the 3 groups on continuous aging variables and cardiometabolic risk factors (eg, age at baseline). The chi-square statistic was used for categorical variables, including biographic characteristics (eg, sex, race/ethnicity) and the portion of participants who fell outside of normal limits on cardiometabolic risk.

Primary analysis

As in the attrition analysis, the chi-square statistic was used to compare the sex and race/ethnicity categories for the portion of participants who fell outside of normal limits on cardiometabolic risk. The McNemar test was used to determine significance of changes in proportions. To identify predictors of diabetes at follow-up, simple bivariate linear regression was used. Although point-biserial correlations would have been more appropriate given that diabetes status is dichotomous, a standard Pearson product correlation is usually close in value to a point-biserial correlation.

Results

Sample characteristics

Sample characteristics are shown in **Table 2**. The average age at the time of the follow-up exam was 51.3 years and the average duration of injury at follow-up was 27.3 years. The distribution of general SCI deficits across race/ethnicity showed substantial differences in both the full cohort baseline sample and the respondent baseline sample. Whites in both samples were more impaired. Of the Whites in the full cohort baseline sample, 62.7% had tetraplegia compared to 40.4% of Hispanics and 39.1% of Blacks. Similarly, of the Whites in the respondent baseline sample, 70.0% had tetraplegia compared to 37.1% of Hispanics and 30.8% of Blacks.

Table 2. Participant characteristics grouped by sex for the full cohort baseline sample, the reduced respondent baseline sample, and the follow-up sample

	Full cohort baseline ($N = 845$)		Respondent baseline ($n = 150$)		Follow-up[a] ($N = 150$)	
Characteristics	**Men (85.9%)**	**Women (14.1%)**	**Men (82.7%)**	**Women (17.3%)**	**Men**	**Women**
Mean time to follow-up ± *SD*, years	—[b]	—	—	—	15.6 ± 0.8	15.9 ± 0.9
Follow-up range, years	—	—	—	—	13.9–17.9	14.0–17.8
Mean age ± *SD*, years	37.0 ± 10.9	41.5 ± 12.6	34.8 ± 8.4	37.0 ± 9.6	50.5 ± 8.3	52.9 ± 9.3
Age range, years	18.0–78.2	20.5–77.2	20.7–62.5	20.7–62.5	35.8–77.3	38.3–73.1
Mean injury duration ± *SD*, years	12.1 ± 8.4	14.7 ± 10.5	11.0 ± 7.0	13.2 ± 7.9	26.7 ± 6.8	29.1 ± 7.9
Duration range, years	1.1–56.7	1.4–46.3	1.4–38.7	1.4–30.8	16.8–52.9	17.3–47.2
Hispanic %	50.5	41.3	62.1	46.2	—[c]	—
White %	24.1	22.9	20.2	19.2	—	—
Black %	22.3	28.4	14.5	30.8	—	—
Asian %	2.0	5.5	2.4	0.0	—	—
Other %	1.2	1.8	0.8	3.8	—	—

[a]Average ± *SD* years to follow-up was 15.7 ± 0.9.
[b]Not applicable.
[c]Duplication of racial/ethnicity percentage is omitted for clarity.

In the full cohort baseline sample, both Hispanics and Blacks were significantly younger than Whites (35.8 and 36.8 vs 42.1 years, respectively; $P < .05$), with fewer years post injury (Hispanics, 10.6; Blacks, 10.8; Whites, 17.8). In contrast, the respondent baseline sample showed no significant differences in age or injury duration between men and women or between racial/ethnic groups.

Attrition

Those who were deceased by follow-up were older at the time of injury (deceased were 30.6, participants were 23.8, and nonrespondents were 24.5 years old, on average) and at enrollment (deceased, 47.7; participants, 35.2; nonrespondents, 35.8 years, on average), and had lived more years post injury (deceased, 17.2; participants, 11.4; nonrespondents, 11.3 years, on average). The percentage of Whites was highest among those deceased (37.3% compared with 20% for participants and 20.3% for nonrespondents). Of the cardiometabolic risk factors and other indicators, only fasting plasma glucose was significantly different, both when measured over time (mean mg/dL: deceased, 98.7; participants, 91.1; nonrespondents, 93.6) and in the percentage of individuals who exceeded the cutoff (deceased, 26.9%; participants, 12.7%; nonrespondents, 20.9%).

Natural progression of cardiometabolic syndrome

Over the approximately 17 years from the respondent baseline sample to the follow-up sample, the frequency of cardiometabolic syndrome increased from 6.7% to 20.8% or 38.2% depending on the 2 diagnostic definitions used in the follow-up ($P < .001$, in both cases) (**Table 1**). Measurements of body mass index (BMI) and waist circumference in the follow-up sample revealed the presence of risk factors in over 40% of participants, which is similar to the general population.[24]

As determined by BMI, glucose, triglycerides, and HDL measures, Hispanics had a markedly higher frequency of cardiometabolic syndrome in both the full cohort baseline sample and the follow-up sample (58.7% and 57.9%; $P < .001$, in both cases) (**Table 3**). In comparison, Whites at follow-up had a markedly lower frequency of cardiometabolic syndrome (12.3%) compared to the full cohort baseline sample (22.8%), but this difference was not significant (**Table 3**).

Figure 1 shows sex differences for frequency of cardiometabolic syndrome. The assessment named "Follow-up Plus" added 2 measures for diagnosis of cardiometabolic syndrome (**Table 1**). Waist circumference was measured for the central obesity risk factor and blood pressure was

Table 3. Percentage of participants with cardiometabolic syndrome grouped by race/ethnicity, showing marked disparity for Hispanics

	Full cohort baseline (*N* = 845)	Follow-up[a] (*N* = 150)
Hispanic	58.7	57.9
White	22.8	12.3
Black	13.0	21.1
Other	3.3	3.5
Asian	2.2	5.3

Note: Cardiometabolic syndrome was defined by having any combination of 3 of the 4 risk factors available in the respondent baseline sample (see **Table 1**).

[a]Average ± *SD* years to follow-up was 15.7 ± 0.9.

measured as a fifth risk factor for determination of cardiometabolic syndrome at follow-up only. As a result, 2 alternative definitions of cardiometabolic syndrome were used for comparison, with the more limited determination made for the respondent baseline sample. When defined by having any combination of 3 of the 4 risk factors measured in the respondent baseline sample, and using BMI only (**Figure 1**, "Follow-up"), no substantial difference was found between men and women. However, when defined by having any combination of 3 of the 5 risk factors measured at follow-up, and including waist circumference to determine central obesity in either of 2 ways (**Figure 1**, "Follow-up Plus"), women showed a markedly greater increase in percentage than did men. Although the increase in frequency of cardiometabolic syndrome in women at follow-up was evidently greater than the increase seen in men, this difference was not statistically significant for this small group of 26 women.

Natural progression of diabetes

The frequency of overt diabetes, as defined by fasting glucose values of >126 mg/dL, increased by a factor of 6.7 from the respondent baseline (3.3%) to follow-up (22.2%). In comparison, in the full cohort baseline sample measured 17 years earlier, the percentage of participants with fasting glucose values of >126 mg/dL was 5.7%.

There were no significant differences in diabetes status between sexes or between races/ethnicities within the full cohort baseline sample, the respondent baseline sample, or the follow-up sample, including when the second definition of diabetes was used. Diabetes defined by fasting glucose of >126 mg/dL was apparent in 5 cases of the 150 respondents at baseline. At follow-up, using only the fasting glucose criterion, 3 of the 5 participants initially diagnosed as diabetic no

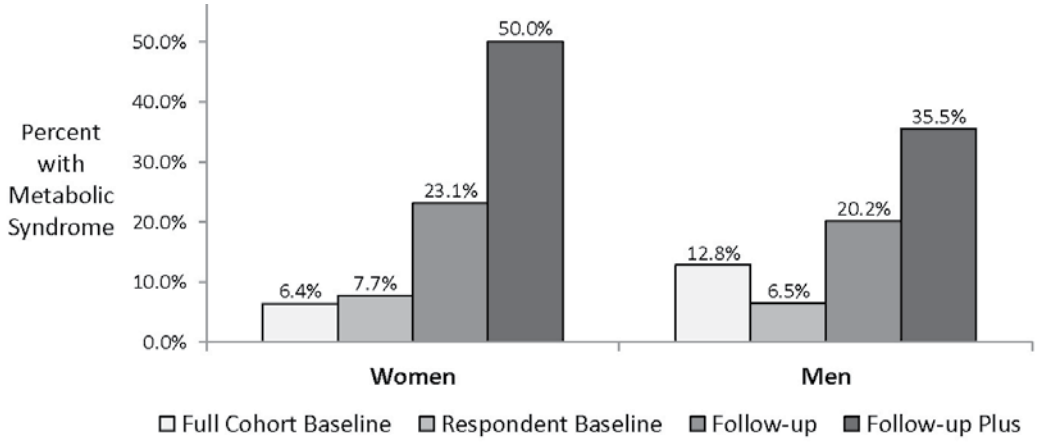

Figure 1. Increase in the frequency of cardiometabolic syndrome after an average of 15.7 ± 0.9 (*SD*) years, grouped by sex, showing marked disparity by sex when using the revised definition of the syndrome. Follow-up Plus = revised definition and added measure for diagnosis of the syndrome. The percentage with cardiometabolic syndrome in each sample is shown above the data bar. Full Cohort Baseline, *N* = 845 (men 85.9%, women 14.1%); Respondent Baseline/Follow-up/Follow-up Plus, *N* = 150 (men 82.7%, women 15.9%).

longer met the diagnosis; 2 of the 5 continued to meet the fasting glucose diagnosis; and 21 of the 145 (14.5%) initially not meeting the fasting glucose diagnosis met the diagnosis at follow-up. Alternatively, for diabetes defined using the fasting glucose, hemoglobin A1c, or medication criteria, 2 of the 5 participants initially diagnosed as diabetic met none of the criteria; 3 of the 5 met at least one of the criteria; and 31 of the 145 (21.4%) initially not meeting the fasting glucose diagnosis met at least one of the diabetes criteria at follow-up ($P < .05$).

At follow-up, BMI and waist circumference were moderately and very significantly correlated with diabetes status (BMI with diabetes status, $r = .2519$, $P = .001$; waist circumference with diabetes status, $r = .2089$, $P = .006$). For the correlation analysis, diabetes status was defined using the fasting glucose, hemoglobin A1c, or medication criteria.

Discussion

Our results identify the magnitude of changes in cardiometabolic syndrome and overt diabetes status over 17 years in people with chronic SCI and reveal how these changes relate to racial/ethnic and sex demographics. As expected, we found a marked and clinically important increase in both cardiometabolic syndrome and overt diabetes status after 17 years of living with SCI. In addition, 2 possible disparities were found. Hispanic participants had a much higher frequency of cardiometabolic syndrome (**Table 3**), which was highly significant ($P < .001$), despite being on average less impaired than Whites with consequently greater capacities for mobility and exercise. For women, a possible disparity in frequency of cardiometabolic syndrome was found on follow-up when using the enhanced measures and definition of the syndrome, but this was not significant. Diabetes status did not show obvious disparities, which is supported by previous findings on glucose tolerance in SCI.[3]

Interpretation of our findings on racial disparity is affected by a demographic confounder. Hispanics and Blacks in the respondent baseline sample were less impaired than Whites. This difference may be expected because race/ethnicity is associated with disparities in access to services, which increase the risk of early mortality after SCI.[25,26] As a result of this selection effect, an increased percentage of Hispanic participants with better outcomes appeared in the full cohort baseline sample and consequently had a greater survival rate thereafter (and a larger number of participants at follow-up). However, this confounder would not decrease the magnitude of the large Hispanic disparity in cardiometabolic syndrome; on the contrary, it would increase the magnitude of the disparity when adjustment is made for the degree of impairment.[3,4] Therefore this disparity is likely to be substantially underestimated. Indeed, the possible clinical importance of this disparity among persons with SCI is emphasized by findings among the able-bodied, where Hispanic people have rates of cardiovascular disease similar to those of Whites.[16]

Interpretation of our findings on cardiometabolic changes for women is uncertain, and we propose that a larger study on the progression of cardiometabolic disease in women with SCI is thereby warranted. A progression of cardiometabolic syndrome with aging in women with SCI would be consistent with a report showing that able-bodied women develop atherosclerosis later than do able-bodied men.[27] Findings from studies of men with SCI cannot necessarily be applied to women with SCI. For example, in men with SCI, physical activity is correlated with levels of HDL, but this correlation is not found for women with SCI.[28,29] Indeed, the findings of one of our previous cardiovascular studies on asymptomatic women with SCI provides strong data on a surrogate clinical endpoint that supports disparities in cardiovascular disease for White and Black women with SCI compared to White and Black women without SCI.[30,31]

It is important to know the genetic factors that could influence these findings. Traditional risk factors explain the majority of the differences in mortality from cardiovascular disease among racial/ethnic groups and between sexes in the United States.[16] The exceptions to this explanation are Black women, Pacific Islanders, and Hispanics. Compared to Whites, Black women and Pacific Islanders have higher mortality from cardiovascular

disease than expected from risk factors alone, whereas Hispanics have lower mortality than expected.[16] The possible causes of these differences include environment and social factors in addition to genetic susceptibilities. Genetic susceptibilities for cardiometabolic syndrome among families with type-2 diabetes show heterogeneity in the associated genes between racial/ethnic groups.[32]

For Blacks, prognosis is complicated by contradictory effects that are largely genetic in origin.[33-35] Blacks have higher levels of protective HDL than do Whites and Hispanics, in both able-bodied and SCI populations,[33] yet Blacks have higher mortality from cardiovascular disease.[16] The reason for this unexpected relationship appears to be a genetic difference that confers a higher level of lipoprotein(a) in Blacks, including those with SCI.[33] Lipoprotein(a) is an established, independent risk factor for cardiovascular disease[36] that is not currently included in the definition of cardiometabolic syndrome. Consequently, the risk of cardiovascular disease for Blacks is underestimated when determined by the frequency of cardiometabolic syndrome. Therefore, although the 22 Black participants in our study showed only a moderate increase in cardiometabolic syndrome at follow-up, Blacks with SCI may nevertheless face a much higher risk for cardiovascular disease as the result of genetic differences.

Finally, we found that BMI and waist circumference are possible discriminators for overt diabetes. In comparison to our observations, it has been previously reported by other researchers that waist circumference is a predictor of fasting plasma glucose levels in asymptomatic individuals but that BMI is not a predictor.[37] However, the previously reported study used a continuous variable of fasting glucose levels, whereas our study used a categorical variable (diabetes or not diabetes), with diabetes status defined using 2 additional criteria (hemoglobin A1c and medications), and included participants with overt diabetes. Another source of difference is that correlations between abdominal fat and BMI for those with SCI vary considerably depending on neurological deficit, with lower correlations among those with incomplete injuries.[30] The majority of participants in our study were neurologically complete, whereas the previously published study included 27 individuals with a range of levels and completeness of injury.

In the general population, BMI and waist circumference are used to estimate intra-abdominal fat, which is the underlying physiological risk factor for cardiometabolic conditions. For the general population, waist circumference is usually preferred because short, very muscular individuals generally have high BMIs with fewer cardiometabolic conditions. In individuals with SCI, BMI can be more difficult to measure, and both BMI and waist circumference underestimate obesity in SCI.[23,38-40] However, although BMI and waist circumference are not good estimators of intra-abdominal fat for persons with SCI, our finding suggests that these 2 measures should be further investigated in the aging SCI population as discriminators of diabetes.

Clinical implications

The implication of these findings for developing best practices for rehabilitation is that clinical practice guidelines need to be customized for people with SCI, and rehabilitation professionals need to gain a better understanding of the reported demographic disparities. Some progress is being made. First, differences in patterns of activities between men and women and between racial/ethnic groups with SCI have been reported and reviewed.[41] Second, updated recommendations for pharmacotherapies for cardiometabolic syndrome in persons with SCI and customized combination strategies of exercise and diet have been reported and reviewed.[42] Third, female-specific, evidence-based guidelines from the American Heart Association for prevention of cardiovascular disease in women[42] reflect the specific aspects of cardiovascular disease for women. Finally, a specific pharmacological treatment for dyslipidemia in persons living with SCI has recently been assessed in a rigorously designed clinical trial.[44] Application of evidence-based methods such as these, combined with better understanding of the natural progression of cardiometabolic syndrome and demographic disparities in people aging with SCI, are needed to establish customized clinical practice guidelines for this growing population.

Limitations

There are several noteworthy study limitations. First, the attrition rate was high after 17 years. The attrition analyses help to identify how the selected attrition may have affected the study results. Second, the number of indicators of cardiometabolic syndrome differed between the 2 assessment points. This necessitated additional analyses using the restricted and more complete data sets.

Conclusion

There was a clinically important increase over time in the frequency of cardiometabolic syndrome in individuals aging with SCI, especially among Hispanic people and women, and a similar increase in overt diabetes.

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